REMARKS

I. Status of the Claims

Claims 2-20 are pending in the application, and claims 7 and 9-18 stand withdrawn pursuant to a restriction requirement. Therefore, claims 2-6, 8, 19 and 20 are under consideration and stand rejected under 35 U.S.C. §112, second paragraph and/or 35 U.S.C. §102. The specific grounds for rejection, and applicants' response thereto, are set out in detail below.

New claims 21-24 are equivalent to pending, but non-elected, claims 9, 11, 12 and 13. It is clear from page 6, lines 4-9 of the corresponding PCT application that the present application discloses the presently claimed methods of treatment for individuals that have already been determined to be 'at risk' of developing or progression of cardiovascular disease.

II. Rejection under 35 U.S.C. §112, Second Paragraph

Claims 4 and 6 are rejected as indefinite. Applicants have provided amendments addressing the perceived antecedent basis issues. Therefore, applicants believe the rejections are overcome, and reconsideration and withdrawal of the rejections is therefore respectfully requested.

III. Rejection under 35 U.S.C. §102

The examiner has rejected Claims 2-6, 8 and 19-20 under §102 as allegedly being anticipated by paragraphs [0017], [0019], [0059], [0060], [0062] and [0063] of Witztum *et al.* (US 2007/0122419 A1; hereinafter "Witztum"). The present claims are allegedly anticipated by the disclosure in the aforementioned paragraphs which, according to the examiner, teaches "a method for treating of a human against atherosclerosis comprising administering a

pharmaceutical composition comprising an antibody specific to a phosphorylcholine (PC)." Applicants respectfully traverse.

Applicants submit that the examiner's allegation is based on the incorrect assumption that disclosure in paragraphs [0017], [0019], [0059], [0060], [0062] and [0063] of Witztum of antibodies that bind to and/or raised against oxidized low density lipoprotein (OxLDL) should be construed as being the same as a disclosure of antibodies with binding specificity to PC, a recited in the rejected claims. However, for the reasons discussed below, this is incorrect.

First, applicants point out that claims 2 and 8 have been amended to more clearly define the claimed invention. Both of these claims now recite "an antibody preparation with specificity to a phosphorylcholine conjugate, wherein said preparation is a preparation of monoclonal antibodies with specificity for a phosphorylcholine conjugate or a subfraction of human immunoglobulin selected for the ability to bind to a phosphorylcholine conjugate" (underlined material added by the present amendment).

Support for the one aspect of the amendment may be found for example, in the specification, at page 4, lines 16-20, which passage refers to using an "antibody preparation, for example a monoclonal antibody, with specificity to a phosphorylcholine conjugate." Thus, the claims are now defined, one aspect, as a monoclonal antibody preparation with the defined specificity.

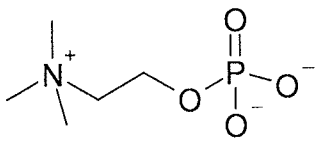
Further support is provided at page 9, line 20 to page 10, lines 8, which describes "a subfraction with aPC activity of a human immunoglobulin preparation" that can be prepared from various available human antibody preparations. Thus, clearly a sub-fraction of antibodies that is specifically selected for its ability to bind PC is supported as well. Also, see page 27, lines 1-13 (describing the preparation of sub-fractions of anti-PC antibodies).

Thus, these passages, and the corresponding new claim language, support the construction of the claimed subject matter as a ***preparation as a whole*** having specificity towards a PC conjugate, rather than referring to ***any*** antibody preparation so long as it merely happens to contain ***some*** antibodies that can bind to PC without needing the preparation itself to show overall specificity towards PC. However, as explained further below, there is no disclosure in Witztum of an antibody preparation where ***the preparation as a whole*** has binding specificity to PC.

A. The Antibodies of Witztum

The examiner alleges that paragraphs [0017], [0019], [0059], [0060], [0062] and [0063] of Witztum teach "a pharmaceutical composition comprising an antibody specific to a phosphorylcholine (PC)." As stated above, applicants submit that this allegation is based on an assumption that disclosure in paragraphs [0017], [0019], [0059], [0060], [0062] and [0063] of Witztum of antibodies that bind to and/or raised against oxidized low density lipoprotein (OxLDL) should be construed as being the same as a disclosure of antibodies with binding specificity to PC. Also, as stated above, such an assumption is incorrect:

- PC is a small molecule (molecular mass 184) having the following structure:



- By contrast, OxLDL is a large and highly complex multi-component macromolecule. It contains a single apolipoprotein B-100 molecule (Apo B-100, a glycoprotein with 4536 amino acid residues), a highly-hydrophobic core consisting of polyunsaturated fatty acid known as linoleate and about 1500 esterified cholesterol molecules. This

core is surrounded by a shell of phospholipids and unesterified cholesterol, as well as the Apo B-100 protein. OxLDL particles are approximately 22 nm in diameter and have a mass of about 3 million daltons. The structure of non-oxidised version, LDL, is further discussed in paragraph [0036] of Witztum. It is further noted that the ApoB-100 component of OxLDL is a glycoprotein that comprises 4-10% by weight carbohydrate and the lipid components of OxLDL also contain carbohydrates (La Belle & Krauss, 1990, J. Lipid Res., 31, 1577-1588; see abstract and, in particular page 1578, cols. 1-2)

In immunological terms, there simply is no comparison between the simple and tiny PC molecule (molecular mass 184) and the highly complex, enormous, multi-component OxLDL particle (3 million daltons) that contains a mixture of protein, many linoleate and cholesterol molecules and other phospholipids, and extensive carbohydrate components.

OxLDL comprises, as just one of its many components, phospholipids that carry a PC moiety. That does not mean, however, that antibodies raised against OxLDL will necessarily bind to those PC moieties. Antibodies raised against OxLDL could be – and in fact would be expected to be – reactive to any one of a virtually ***infinite*** number of different epitopes on the OxLDL molecule. Even taking the Apo B-100 protein component of OxLDL alone, it is a protein of 4536 amino acid residues that is extensively glycosylated and represents a virtually unlimited number of different amino acid and/or carbohydrate epitopes that could be bound by an anti-OxLDL antibody. Thus, merely stating that an antibody is raised against, or reactive to, OxLDL cannot be taken as a disclosure, or even a suggestion, that the same antibody is in particular reactive with PC.

To put it another way, it may be true that antibodies to PC can bind to OxLDL because OxLDL contains an exposed PC epitope, but the reverse is not inevitably true, *i.e.*, one cannot conclude that an antibody that is raised against, or that binds to, OxLDL will necessarily also

bind to PC. Rather, it could bind to any one of the virtually infinite number of different other epitopes presented by OxLDL. In fact, the present application provides ***direct evidence*** that antibodies that bind to OxLDL are not necessarily antibodies that bind to PC. Indeed, page 17, lines 12-16 of the published PCT application (WO 2005/100405) upon which the present application is based reports that "aPC IgM levels correlated negatively with IMT (Rho 0.18, p=0.006).... Unlike aPC IgM, aOxLDL and aMDA-LDL did not reach significance in these determinations." In the foregoing passage, antibodies to PC are referred to as "aPC" and antibodies to OxLDL are referred to as "aOxLDL"; "IMT" refers to intimal-medial thickness which is an indication of the progression of atherosclerosis (see page 16, lines 2-6 of the published PCT application).

The above-quoted passage clearly shows that the statistical correlation between the progression of atherosclerosis in humans and levels of IgM antibodies that bind PC ("aPC") is significant, whereas there is no statistically significant correlation with levels of antibodies against OxLDL ("aOxLDL"). The only possible explanation for the observed difference is that antibodies against PC represent a ***different antibody population*** as compared to antibodies against OxLDL in humans. This is direct proof that disclosure of antibodies reactive to OxLDL cannot be taken as a disclosure of an antibody that is reactive with PC in particular.

In effect, this rejection is one based on "inherency" as the reference clearly does not establish that the antibody preparations as disclosed have specificity for PC. However, the law on inherency is quite clear that mere possibilities are insufficient to establish anticipation – it is required that the prior art provide with ***certainty*** that the claimed subject matter existed. *In re Rijckaert*, 9 F.3d 1531, 1534, 28 USPQ2d 1955, 1957 (Fed. Cir. 1993); *In re Oelrich*, 666 F.2d 578, 581-82, 212 USPQ 323, 326 (CCPA 1981) ("To establish inherency, the extrinsic evidence

'must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill. Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient."); *In re Robertson*, 169 F.3d 743, 745, 49 USPQ2d 1949, 1950-51 (Fed. Cir. 1999). Here, for the reasons given above, no such certainty exists.

B. The Antibody Preparation of the Present Claims

The claims as presented for reconsideration are directed to methods that use "an antibody preparation with specificity to a phosphorylcholine conjugate, wherein said preparation is a preparation of monoclonal antibodies with specificity for a phosphorylcholine conjugate or a subfraction of human immunoglobulin selected for the ability to bind to a phosphorylcholine conjugate." An monoclonal antibody preparation that has binding specificity to a PC conjugate is not the same as an antibody preparation, for example, raised against OxLDL that will contain a mixture of antibodies with specificity for large variety of different epitopes on the highly complex OxLDL molecule. Even if the anti-oxLDL preparation did contain ***some*** antibodies with binding specificity to PC, one could not reasonably argue that the ***entire*** preparation had specificity to a phosphorylcholine conjugate. The same applies to antibody preparations raised against any other large and complex antigens that contain a multitude of potential epitopes.

Applicants submit that there is no disclosure in Witztum of an antibody preparation where ***the entire preparation*** has binding specificity to a phosphorylcholine conjugate. Indeed, there is ***clear and direct evidence*** in Fig. 1(c) of Witztum that its antibody preparations do not have binding specificity for PC. As discussed in paragraph [0024] of Witztum, this figure shows the properties of an antibody preparation that results from pneumococcal immunization which

the authors have used to produce "anti-OxLDL IgM antibodies." A clearer version of Fig. 1(c) is to be found, also as Fig. 1(c), in Binder *et al.*, 2003, *Nature Medicine*, **9**(6), 736-743 (previously submitted IDS). This figure shows the ability of various molecules to interfere (*i.e.*, compete) with the binding of this antibody preparation to an OxLDL ligand. As will be apparent, even the non-oxidized form, LDL, in which PC is ***not*** exposed, can reduce binding by 5-10%; likewise MDA-LDL, again in which PC is ***not*** exposed, can reduce binding by almost 20%, and KLH in which no PC is present at all, can reduce binding by around 30%. This clearly indicates that the antibody preparations generated by Witztum possess considerable cross-reactivity that would not be related to PC, and thus fail to meet the "monoclonal" recitation of the current claims. Similarly, this would also exclude an antibody preparation where the preparation is an antibody "subfraction with aPC activity," also as presently recited. In sum, there simply is no way to confuse the antibody preparations of the reference with those as now claimed.

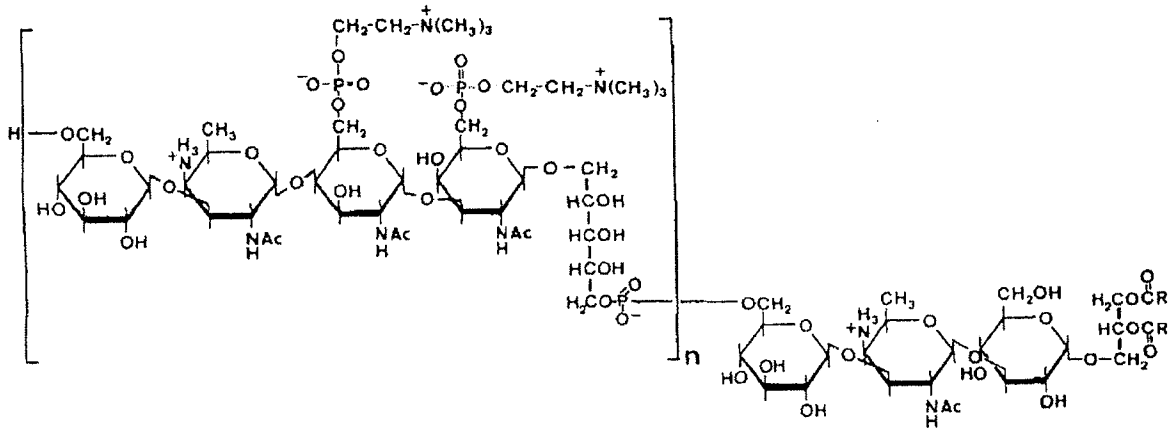
Turning to the particular paragraphs [0017], [0019], [0059], [0060], [0062] and [0063] cited by the examiner as being allegedly relevant to the present claims, applicants respectfully submit that the disclosures in these paragraphs do not indicate anticipation of the presently claimed invention.

Paragraph [0017]:

This paragraph refers to the administration of "antibodies that bind to oxidised low density lipoprotein (OxLDL)". These antibodies could bind to any epitope on OxLDL and paragraph [0017] is entirely non-specific on the matter. For these reasons, this is not a disclosure of any antibodies that bind to PC in particular, much less a preparation wherein the preparation *as a whole* has binding specificity to PC.

Paragraph [0017] goes on to state that the "antibodies can result from an immunogenic response to phosphorylcholine-containing lipoteichoic acid components of a cell wall

polysaccharide of a pathogen". As shown in Fig. 10 of Behr *et al.*, 1992, Eur. J. Biochem., 207, 1063-1075 (attached), and reproduced below, pneumococcal lipoteichoic acid (LTA) has the following structure:



Thus, compared to PC, pneumococcal LTA is again an enormous molecule that comprises multiple potential epitopes that are entirely unrelated to PC. In particular, and like OxLDL, LTA contains extensive carbohydrate content that can present multiple epitopes when raising an immune response. Therefore, disclosure in paragraph [0017] of Witztum et al of antibodies raised in response to LTA cannot be taken to be a direct, or even implicit, disclosure of antibodies that would necessarily bind to PC, much less a preparation wherein the preparation *as a whole* has binding specificity to PC. Accordingly, the present claims are not anticipated by the disclosures of paragraph [0017].

Paragraph [0019]:

This paragraph does not teach or suggest the administration of any antibodies to a patient. Rather, it discloses the administration of a vaccine that prompts the patient to produce its own antibodies. Thus, it is clear that the disclosure of paragraph [0019] cannot anticipate the present claims, since the present claims require the administration of a preparation that comprises antibodies. Accordingly, the present claims are not anticipated by the disclosures of paragraph [0019].

Paragraph [0059]:

This paragraph reports that "an antibody is raised against phosphorylcholine containing OxLDL derived from a pathogen". The fact that the immunogen used, namely "OxLDL derived from a pathogen", may contain PC, is no indication that the antibody raised will bind to PC at all, for the reasons discussed fully above. This is also clear from the final sentence of paragraph [0059] "*The antibody of the invention is an antibody raised against oxidized LDL*".

This paragraph neither teaches, nor suggests, that antibody that is raised should be one that binds PC specifically; it could bind any other epitope on OxLDL. Certainly there is no teaching or suggestion in this paragraph that teaches a preparation wherein the preparation *as a whole* has binding specificity to PC. Accordingly, the present claims are not anticipated by the disclosures of paragraph [0059].

Paragraph [0060]:

This paragraph discusses ways of administering "antibodies according to the invention"; it is clear from the preceding statement in paragraph [0059] that these are antibodies raised against oxidized LDL. There is nothing in paragraph [0060] that allows the reader to conclude that the antibodies discussed in paragraph [0059] are those that specifically bind to PC.

On the contrary, paragraph [0060] teaches that "Immunization of a human host with OxLDL from a pathogen such a *S. pneumoniae* is one available method. Alternatively, mice or other lower mammals are immunized, and the genes encoding the variable regions of the antibodies specific for the present OxLDL from atherosclerotic tissue and OxLDL from a pathogen are isolated...". Neither of these statements define an antibody beyond the fact that it is taught to be raised in response to, or to bind to, OxLDL, and so paragraph [0060] also fails to specifically disclosure an antibody with binding specificity to PC. Accordingly, the present claims are not anticipated by the disclosures of paragraph [0060].

Paragraphs [0062] and [0063]:

These paragraphs make no further comment on the nature of antibodies to be used, and so add nothing of further relevance. Paragraph [0062] discusses possible routes of administration and options and additives for formulating therapeutic preparations. Paragraph [0063] likewise discusses possible additives in such compositions. Accordingly, the present claims are not anticipated by the disclosures of either of paragraphs[0062] or [0063].

C. Conclusion

Thus, there is nothing in any of paragraphs [0017], [0019], [0059], [0060], [0062] and [0063] that are prejudicial to the novelty of claims 2-6, 8 and 19-20 as presented for reconsideration, and applicants request that the examiner favorably reconsider the matter.

D. New Claims 21–24

New claims 21-24 are dependent on claim 2 and thus are distinguished over the teaching of Witztum for at least the same reasons as given above for claim 2. Furthermore, there is nothing in Witztum to teach or suggest that a risk of developing or progressing cardiovascular disease could be determined in a human by assessing the level of antibodies reactive with a phosphorylcholine conjugate.

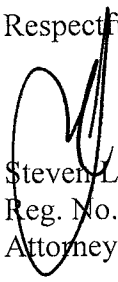
The present application represents the very first teaching and direct evidence that risk of cardiovascular disease could be determined in humans in this manner. New claims 21-24 refer to treating individuals that have been determined to be at risk by this new method. This defines the treatment of a particular patient group that could not have been generated without the use of the

new method of determining risk as provided by the present application. Accordingly, there is nothing in Witztum that prejudices claims 21-24 pursuant to 35 U.S.C. §102(e).

IV. Conclusion

In light of the foregoing, applicants respectfully submit that all claims are in condition for allowance, and an early notification to that effect is earnestly solicited. Should the examiner have any questions regarding this response, a telephone call to the undersigned is invited.

Respectfully submitted,



Steven L. Highlander
Reg. No. 37,642
Attorney for Applicants

FULBRIGHT & JAWORSKI L.L.P.
600 Congress Avenue, Suite 2400
Austin, Texas 78701
(512) 474-5201

Date: November 2, 2010